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Quantitative Risk Assessment: Report of the Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board [1,2,3,4]

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Sheldon W. Samuels [5] *and* **Richard H. Adamson,** *Ph.D.* [6,7]

The present report is essentially an expansion of the items the Subcommittee agreed upon during the November 15, 1982, meeting in response to five questions posed by the Chair: *a*) Definition of QRA as distinct from qualitative risk assessment. *b*) Which models or paradigms of QRA have been, are, or are likely to be heuristic in terms of data fit, testability, and predictive experience? *c*) Is QRA practical in terms of data adequacy of both dose and effects? *d*) Are the regulatory issues that involve QRA separable from the scientific problems of QRA? *e*) Who should do QRA?

The Subcommittee on Environmental Carcinogenesis met four times (August 10, 1982; September 23, 1982; November 15, 1982; and April 25, 1983) to gather information and views for development of a policy on QRA to be adopted by the NCAB. During these four meetings, information was presented by invited speakers from academic medicine, the regulatory agencies, NIH, NAS, and industry. Subsequent to these meetings, letters, reprints, and information on various issues pertaining to QRA (*1–7*) were mailed to the Executive Secretary and/or the Chairman of the Subcommittee and were made available to the Subcommittee. The meetings have been summarized in the minutes, and reprints made available during the meetings were appended to the minutes. In addition, the meetings were summarized in an interim report of the Chairman given to the NCAB on February 1, 1983. These minutes and the interim report are available from the Executive Secretary of the Subcommittee Dr. Richard H. Adamson.

QUANTITATIVE RISK ASSESSMENT

QRA is defined as the assessment of both hazard and exposure information for purposes of estimating the likelihood that hazards associated with the substance will be realized in exposed individuals or populations. This assessment involves two steps. The first is hazard identification–characterization in which toxicity to humans as determined from observations on human populations and/or from experimental systems is characterized. The second step, termed "quantitative risk estimation," is the process by which the risk of disease or death in a population exposed to a toxic agent is related quantitatively to the pattern of exposure, including factors such as the intensity and duration of exposure. In QRA it is essential that both hazard and exposure information be considered. The quantitative process also includes an estimation of uncertainties.

In evaluating the risk of exposure to a particular agent, the first step is to consider the qualitative evidence that the agent is likely to be a carcinogen in humans. This evaluation relies on information from a variety of areas, including epidemiology. Epidemiologic studies provide important information about carcinogenic effects in humans because they associate human cancer incidence with exposure to particular chemicals, industrial processes, or life-style factors. Clinical case reports and descriptive studies are of interest, but case-control and cohort studies are of greater value.

Another source of information on the carcinogenicity of chemicals is long-term animal toxicology studies, in particular the rodent bioassay. Identification of a sub-

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ABBREVIATIONS USED: CEQ=Council on Environmental Quality; DHHS=Department of Health and Human Services; EPA=Environmental Protection Agency; FDA=Food and Drug Administration; IARC=International Agency for Research on Cancer; NAS=National Academy of Sciences; NCAB=National Cancer Advisory Board; NCI=National Cancer Institute; NIEHS=National Institute of Environmental Health Sciences; NIH=National Institutes of Health; NIOSH=National Institute for Occupational Safety and Health; NOAA=National Oceanographic and Atmospheric Administration; NSF=National Science Foundation; NTP=National Toxicology Program; OSHA=Occupational Safety and Health Administration; QRA=quantitative risk assessment; RFA=Requests for Applications.

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[1] Received November 6, 1984; accepted November 6, 1984.

[2] Subcommittee members were Mrs. Angel Bradley, Dr. Roswell Boutwell, Dr. William Powers, Dr. Janet Rowley, Mr. Sheldon Samuels, Dr. Irving J. Selikoff, Dr. Philippe Shubik, and Dr. Gerald Wogan. Ex-officio members were Dr. Tim L. Carter, Dr. Elliott Harris, Dr. Allan Heim, Dr. Peter Preuss, Dr. David Rall, Dr. John Todhunter, and Dr. Ralph Yodaiken.

[3] This report was adopted by the National Cancer Advisory Board by mail ballot on August 15, 1983.

[4] The term "safe" implies freedom from harm and is not used in this document because the concept does not have a scientifically demonstrable basis. Because the term "cause" is commonly associated with the single cause-single effect paradigm, which is not applicable in most analyses of biologic phenomena, this report also avoids the use of that term. The concept of "risk" and "risk factors" should be used both in public and scientific publications in discussions of all toxic agents or processes.

[5] Health, Safety and Environment, Industrial Union Department, 815 16th St., N.W., Washington, DC 20006.

[6] Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, MD 20205.

[7] *Address reprint requests to* Mr. Samuels at the address given in footnote 5 or to Dr. Adamson, Building 31, Room 11A03, National Institutes of Health, Bethesda, MD 20205.

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stance as a carcinogen depends on showing that the test substance causes an increase in the incidence of tumors or a decrease in the latent period.

Additional confirmation of carcinogenicity is provided by positive results observed in more than one animal species, in more than one bioassay, or in different laboratories and by the demonstration that the occurrence of tumors follows a dose-dependent relationship. In animal bioassay studies, factors considered include the increase in tumor incidence in the treated group compared to the incidence in controls, the number of tumors diagnosed per animal, and the percentage of malignant tumors at a given site. Both historical and contemporary control tumor rates are compared with those in the chemically treated group.

Other relevant studies include elucidation of structure-activity relationships, studies on metabolites of the carcinogen, and characterization of chemical and physical properties of the compound. Additional information about carcinogenicity of a compound is also obtained through numerous other studies, including cell transformation, studies on binding to DNA, various genotoxicity assays, and metabolism studies, including those in species in which the long-term animal tests were conducted are compared with metabolism in humans who have been exposed. Most recently, human epithelial cells and tissue explants have been used to provide information on potentially carcinogenic chemicals.

The second step in QRA is exposure assessment, a procedure as important as hazard assessment. Significant progress has been made in mathematical modeling, data monitoring, and laboratory approaches for determining the behavior of chemicals in the environment. Exposure assessment is a highly complex activity because any analysis must take into account various routes of exposure, different concentrations, human activities, biologic conversions, chemical reactions, environmental transport mechanisms, and analytical limitations in the ability to quantify chemicals at trace levels.

When hazard exposure and assessment are completed, the final step, QRA, can be performed. This process applies data from epidemiologic studies, from long-term bioassay studies, and from other sources to describe the relationship between dose of the substance and the probability of toxic response.

The dosage in animal bioassay studies is exaggerated to compensate for the necessarily small study size of animal test systems. For anticipation of effects at low levels, based on what experiments revealed at higher dose levels, the dose-response relationship must be extrapolated into the low-dose region. This region may be orders of magnitude below the dose level used in laboratory studies. Extrapolation from these studies involves the use of various mathematical models. No single model can be universally accepted at the present time. The development and selection of models should be increasingly influenced by an expansion of our knowledge of underlying biologic mechanisms, such as the interaction of carcinogen metabolites and DNA.

The end point in QRA of chemicals for carcinogenicity is a final review and evaluation of hazard and exposure information, taking into account the uncertainties known to exist. The amount and reliability of information available on the numerous parts of an assessment will vary from chemical to chemical. It is important to make decisions about a chemical without overemphasizing any single aspect of the assessment. In addition, it is frequently necessary to make decisions about a chemical when the information available about it is imperfect and/or incomplete.

These uncertainties (and the other uncertainties apparent at each stage of the risk-assessment process) should be clearly and explicitly stated to assist the management of the risks under study.

Moreover, although we are confident that research will reduce the arbitrariness of the selection of assessment methods, it is not probable that the need to make value judgments will be eliminated. The nature of these judgments should also be clearly and explicitly stated.

USES OF QRA

Although the most obvious use of QRA is by the regulatory agencies as one tool in the regulatory process, there are other uses, or potential uses, of QRA. Among these are management of populations at high risk of cancer because of environmental exposure to chemicals and physical agents (e.g., asbestos-related cancer and the economic and social response to it), its use by industry for voluntarily setting priorities in the absence of regulations, and its use by Government, labor, and others to select populations for special programs of medical screening, education, and intervention.

For any use, it must be understood that we are dealing with a primitive application of rough mathematical approximations using data usually generated for other purposes. Those who question the use of QRA for any purpose for most environmental agents make substantive arguments.

The Subcommittee believes, however, that the development and use of this method ought to proceed on the basis of its potential good. Meanwhile, those who manage risk should interpret results obtained using currently available methods of assessment with great caution.

INSTITUTIONAL ARRANGEMENTS OF QRA

One question raised by the Subcommittee was: Who should perform risk assessment? There was general agreement among the members of the Subcommittee, invited guests, and representatives from the regulatory agencies that scientists who perform QRA should be chosen on the basis of their qualifications and should possess expertise in the areas under consideration. In addition, it was believed that while scientists who perform QRA should continue to work both in research and regulatory agencies, an atmosphere that promotes objectivity and sound scientific independence should be

created, i.e., one separated from the regulatory process itself.

The Subcommittee concurred with the NAS, which in its report on risk assessment recommended that the process of risk assessment and risk management should be separated (5). It was also the consensus that the research agencies should continue to try to improve the data base, improve techniques that quantify exposure levels, and continue to develop mathematical procedures applicable to risk assessment. In addition, risk assessments, regardless of where in the Government and by whom they are performed, should be peer reviewed, made available to the scientific community, and subject to comment by the Surgeon General (or the Assistant Secretary for Health).

Circumstances might arise in which a particular institution within the DHHS would have information pertaining to a risk assessment (e.g., bioassay data from the NTP, epidemiology data from NCI, and exposure data from NIOSH) not available to other institutions or agencies. In such a situation, the Surgeon General (or the Assistant Secretary for Health) should be responsible for marshaling whatever resources and individuals in the Government are available to perform a risk assessment.

In situations where originators of data used by the Government for risk assessment are outside the Government research establishment, a special committee (similar to the Clearing House established in previous years by the NCAB with balanced representation for the assessment of NCI bioassays) should be established by the Surgeon General (or the Assistant Secretary for Health) to evaluate the data. Deliberations of this kind should be conducted in meetings open to the public (when legally possible) as peer reviews. Special attention should be given to avoiding conflicts of interest and for protecting proprietary information.

The peer review in place within the NIH is adequate for the purpose of supervising the integrity of the risk-assessment process. When an assessment is challenged, however, a mechanism should be available and used in a manner that will not delay, unreasonably, the use of the assessment. We recognize the fact that the peer review system can fail. Therefore, the responsibility for dealing with challenges must be remanded to the most neutral mechanism, i.e., a panel of career full-time civil servants subject to existing laws governing conflict of interest and access to public information.

APPLICATION AND VALIDITY OF RESEARCH MODELS

The quantitative assessment of human carcinogenic risk from exposure to environmental agents often consists of extrapolating evidence from effects observed under one set of conditions in one population group or biological system to estimate the magnitude of effects expected under a different set of conditions in the human population of interest. This extrapolation involves, in part, mathematical models of the carcinogenic process which are necessarily simplistic representations of a complex biological stochastic process.

One class of these models, dose-response models, are used to describe the presumed mathematical relationship between the level of carcinogenic exposure (the dose) and the magnitude of its carcinogenic effect (the response). These dose-response models fall into two general categories: *a*) tolerance distribution models and *b*) models based on quantitative theories of carcinogenesis or other toxic responses.

The biologic basis for the class of tolerance distribution models assumes that the toxic reaction to a particular stimulus is a deterministic process that depends on an individual's "tolerance level"; a level of the stimulus above this tolerance will produce a specific, singular toxic response with certainty, whereas a stimulus level below this tolerance will produce no response with certainty. Because of variability (both biological and environmental) among members of the exposed population, their tolerance levels will vary, sometimes within quite wide limits, to produce a "smooth" dose-response relationship for the population as a whole. This simple deterministic concept of an individual's tolerance for a particular toxic agent is not likely to provide a reasonable representation of the mechanism of carcinogens which act directly on DNA at the cellular level. However, indirect carcinogenic action (e.g., stimulation of enzymatic action or cell proliferation) may be describable by such models for individuals.

Another class of dose-response models is based on the concept of "hit theory" applied to initiation of the carcinogenic process at the cellular level. Once the cell has been "hit," the process of carcinogenesis is assumed to continue independently of the carcinogenic exposure. These models are axiomatically developed from a theory of the interaction between particles and targets necessary to produce a biologic response. These models were originally derived to explain radiation carcinogenesis, but they have also been used for chemical carcinogens.

A generalization of the single-event hit theory which explains cancer initiation is the multistage, or multi-event, theory that assumes that the carcinogenic process consists of a series of cellular changes. These cellular changes are assumed to be heritable, are characterized as being of slow and improbable occurrence, and may or may not be affected by the particular carcinogen in question. Once a cell has progressed through all the stages, i.e., it has attained its full malignant potential, it then proliferates to a clinically detectable tumor. Other exposure-related risk factors (e.g., proliferation of partially transformed cells) can also be included in the theory. Other theories, based on multiple cells, have also been proposed.

These quantitative theories of carcinogenesis have produced a variety of dose-response models which have different risk-assessment characteristics. Each dose-response model is based on a number of critical assumptions concerning the carcinogenic process. A major limitation of these dose-response models is that their currently untestable assumptions have a significant

impact on carcinogenic risk assessments, and without additional basic knowledge concerning such factors as the mechanism of action, pharmacokinetics, DNA-adduct formation, and so forth, any choice from among these models cannot be made with confidence.

UNCERTAINTIES OF QRA

The uncertainties inherent in QRA are many and varied. High-dose to low-dose extrapolation is the single, most important source of this uncertainty. Assumptions concerning the relationship between exposure level and carcinogenic response are necessary for this extrapolation, since the response rates at low dose levels are often too small to be accurately measured with limited experimental or epidemiologic sample sizes. A quantitative estimate of the risk at a particular low dose level is highly dependent on the mathematical form of the presumed dose-response relationship; differences among models of 3–4 orders of magnitude are not uncommon. More accurate high- to low-dose extrapolations are not possible without knowledge of the mechanism of action, studies on DNA-adduct formation, and information on metabolic disposition of the particular carcinogen in question, since the dose-response relationship is likely to depend on these factors.

Part of the mechanistic knowledge concerns pharmacokinetic information on the fate of the toxic agent once it enters the body. Nonlinear kinetics may be an important determinant of the nonlinear dose response often observed in experimental animal studies conducted at high dose levels. A critical problem in the application of pharmacokinetic principles to low-dose QRA is the potential change in the pharmacodynamics as the level of the toxic agent decreases. The presence of saturation kinetics at high doses may pose problems in QRA based on high-dose experimental results. As an example, the metabolism of inhaled vinyl chloride has been shown to be a saturable process that provides a possible explanation of the nonlinear dose response observed in animal studies. The lack of relevant dose-related pharmacokinetic information adds another measure of uncertainty in QRA within a single species.

QRA across species, commonly referred to as the "mouse-to-man problem," involves potentially more uncertainties than risk assessment within a species. Methodologies for making this animal-to-man extrapolation rest, in part, on pharmacokinetic considerations of species similarities in absorption, distribution, metabolism, and elimination of the chemical carcinogen as well as DNA-adduct formation and DNA repair processes. Although no single experimental animal species mimics man in all respects relevant to the pharmacokinetics of a particular chemical, animal-to-man extrapolation is often made with the critical assumption that all the relevant biological parameters are the same in humans and animals. Unfortunately, often very little is known concerning interspecies variations among these biological parameters, and these potential species differences can make interpretation of animal-to-man extrapolations both uncertain and arbitrary.

In addition, other sources of uncertainty in QRA include: *a*) environmental and genetic heterogeneity and interaction; there are many environmental factors that one may be exposed to through occupation (e.g., asbestos), life-style (e.g., cigarettes), or of intrinsic origin (e.g., hormonal imbalances) which may affect one's response to a particular carcinogenic exposure; *b*) differential effects for exposure rate and duration; the presumed relationship of risk to the rate and duration of exposure can have substantial consequences when quantitatively estimating risk from one exposure situation to another; experimental studies of dose fractionation have shown that no general relationship exists; *c*) reliable epidemiological data only exist for a relatively few agents to which humans are exposed, and generally there is an absence of dose measurement. Also, little information is available on intrauterine exposure; *d*) the identification of agents and effects is obscured by latency factors; *e*) the spectrum of tumors is sometimes overlooked because of a focus on unique associations (e.g., vinyl chloride and angiosarcoma); *f*) diagnostic uncertainties may lead to underdiagnosis; *g*) QRA is expressed in static terms even though a dynamic situation is addressed; and finally, *h*) qualitative factors such as data quality, multiple studies from different sources (e.g., chemical structure-activity and various "mutagenesis" tests), multiple tumors within a single experimental animal species, multiple experimental species-strains giving different qualitative and/or quantitative results, the combination of negative and positive studies, and competing risk all have a potentially important effect on QRA.

The current methodologies for the quantitative assessment of human carcinogenic risk, which can be heuristic in careful applications, rely on necessarily simplistic and currently untestable assumptions. However, as further knowledge of chronic diseases and toxicity mechanisms is acquired, this information should help provide a basis for more precise and more widely applicable quantitative estimates of the risk to humans of environmental carcinogens.

NCI CONTRIBUTION TO RESEARCH RELATED TO RISK ASSESSMENT

The NCI contributes to the development of information on QRA through its activities in the area of information dissemination, by providing advice and expertise to regulatory agencies, and through its efforts in the field of chemical and physical carcinogenesis research, epidemiology, and most recently in the new area of biochemical and molecular epidemiology.

The NCI provides assistance in an informal way to regulatory agencies responsible for performing risk assessments by keeping their staffs abreast of new developments in the area of carcinogenesis research and risk-assessment methodologies. This informal interchange involves providing the agencies with accepted journal articles, reports, and summaries of research findings pertinent to risk assessment; it also includes conferences focusing on issues of importance to risk assessment

which are attended by representatives from NCI, the FDA, NIOSH, and other agencies.

A number of laboratory techniques have been developed or adopted by the NCI intramural research program and by other research institutions to augment classical epidemiologic studies. These techniques, which include cytogenetic studies to detect chromosome aberrations, assessment of carcinogen-DNA adduct formation, studies of sister chromatid exchange, and analysis of urinary and fecal mutagens, can make potentially important contributions to the risk-assessment process. For this reason, the NCI is placing a major emphasis on a new research area called "biochemical and molecular epidemiology." This new area of emphasis consists of multidisciplinary investigations into cancer etiology that combine epidemiologic and experimental approaches. Included are efforts to incorporate already developed biochemical techniques into epidemiologic investigations and the further development and refinement of new experimental procedures into safe, accurate, reliable, and informative adjuncts to human investigations. The primary goal of biochemical epidemiology is to identify individuals at high cancer risk by obtaining pathobiologic evidence of *a*) high exposure of target cells to carcinogens and/or *b*) increased susceptibility due to inherited or acquired host factors.

Currently available techniques exist that would allow the utilization of biochemical measures to better characterize exposure to carcinogens, to serve as intermediate end points on the path to cancer, to identify measures that halt or reverse this process, and to facilitate the risk-assessment process. Included in these investigations would be the following: *a*) efforts to evaluate body burden of chemical carcinogens in studies of occupational and general environmental cancer risk factors; *b*) sophisticated analyses of air, water, and biologic specimens for carcinogenic and mutagenic substances in conjunction with specific analytic studies; *c*) evaluation of disturbances in immune function as they may relate to cancers, particularly those of the hematopoietic system; and *d*) investigation of the relationship between micronutrients and a variety of epithelial cancers. Advances in laboratory methods have been recently developed to be used in combination with analytical epidemiology to identify individuals at high cancer risk. These methods include: *a*) techniques to assess specific host-susceptibility factors; *b*) assays that detect carcinogens in human tissues, cells, and fluids; *c*) cellular assays to measure pathobiologic evidence of exposure to carcinogens; and *d*) methods to measure early biochemical and molecular responses to carcinogens.

Two examples illustrate the potential of this approach. The first is the use of drugs to probe carcinogen metabolism. Most carcinogens require metabolic oxidation to electrophilic reactants to exert their carcinogenic effects. Oxidation is generally via a family of cytochrome P_{450} enzymes that also metabolize endogenous substrates and many drugs. These enzymes are under genetic and environmental control, and their oxidative activities vary widely among individuals. Indicator drugs are now known to be oxidized by specific cytochrome P_{450}'s that are also responsible for the activation of carcinogens; e.g., the antihypertensive drug debrisoquine may be a useful probe for predicting metabolic activation of aflatoxin B_1. Individuals who are rapid metabolizers of such drugs may also be at high cancer risk when exposed to carcinogens that are activated by the same cytochrome P_{450}'s as the indicator drug.

The second example is the use of ultrasensitive enzyme radioimmunoassay to measure carcinogen-DNA adducts. The covalent binding of the activated form of a carcinogen to DNA may be viewed both as a pathobiologic dosimeter of environmental exposure to a carcinogen and as a predictor of an individual's metabolic balance between carcinogen activation and deactivation and his capacity for DNA repair. Ultrasensitive enzyme radioimmunoassays to measure carcinogen-DNA adducts are a hundredfold more sensitive than radioimmunoassays and are now being used in pilot laboratory-epidemiology studies. A wide variation in the amount of this type of genotoxic damage has been found in high-risk groups due to occupation (e.g., foundry workers and asphalt workers) or personal habits (e.g., tobacco smoking). On the basis of an extensive data base from studies in experimental carcinogenesis, individuals with high levels of carcinogen-DNA adducts may be at increased cancer risk.

Scientific opportunities generally arise when two or more research areas converge and/or advances in methodology occur. Research in the laboratory has recently provided us with both critical information on mechanism(s) of carcinogenesis and new technological advancements including those in molecular biology. Epidemiology has clearly demonstrated the importance of environmental exposure to carcinogens. It is now practical to integrate laboratory determinations into more classical epidemiologic approaches to chronic disease. The potential of biochemical and molecular epidemiology to predict cancer risk on an individual and population subset basis, instead of a total population level, and prior to the onset of clinically evident cancer may represent a significant contribution to risk assessment.

The NCI is performing intramural research in this area and is supporting extramural programs through the traditional R01 grant mechanism and through issuance of RFA.

NCI ROLE IN ENVIRONMENTAL CARCINOGENESIS

The NCI's contributions to identification of environmental carcinogens are diverse and include providing staff expertise and advice to regulatory and other agencies and institutions, disseminating information, and performing and supporting research in the areas of epidemiology and chemical and physical carcinogenesis. The Subcommittee thought that these NCI activities in environmental carcinogenesis were appropriate and that they should be continued.

In the 1970's, the NCI pioneered a carcinogenesis

testing program through which scientists established a standardized way to evaluate the carcinogenic activity of chemicals in mice and rats, which seem to be good predictors of chemicals carcinogenic in humans. Of the 30 agents for which there is human evidence that exposure is associated with cancer in humans, all (with the possible exception of arsenic) are risk factors for cancer in laboratory animals.

In 1981, the carcinogenesis testing program was transferred to the NIEHS from NCI, an action that provides for direct management by the NTP of the NIH components of the program. Nevertheless, the NCI maintains a significant level of involvement in the carcinogenesis testing program by nominating chemicals for testing in the bioassay program and by membership on the NTP Executive Committee, which selects the chemicals to be tested.

The NCI also provides advice and the expertise of its staff to other Government agencies, including those with regulatory functions, such as the FDA and OSHA, in the evaluation of data for use in risk assessment. It provides assistance in an informal way to agencies by keeping their staffs apprised of new information and developments in the area of carcinogenesis research. A primary means for broad distribution of research results is the published literature, and the NCI routinely provides the agencies with accepted journal articles, reports, and summaries of new research findings, and in several instances information has been provided prior to publication in the journal literature. In addition, scientists often present preliminary data at scientific meetings prior to publication of final results which may not be available until several months later. Other productive avenues of exchange include conferences convened to discuss particular issues of importance related to environmental carcinogenesis and attended by individuals from NCI, FDA, NIOSH, and other agencies.

In addition, the NCI provides input to NIOSH on occupational and environmental carcinogenesis through members of the Environmental Epidemiology Branch of the Epidemiology and Biostatistics Program, Division of Cancer Etiology. Other NCI staff members serve on panels and committees organized by regulatory and other agencies. For example, NCI staff are members of the Interagency Testing Committee organized to evaluate chemicals covered by the Toxic Substances Control Act. Staff from the NCI also serve as members of the Task Force on Environmental Cancer and Heart and Lung Disease and as members of the Task Force Planning Group which reviews and plans the activities of the Working Group meetings, including preparation of annual reports for Congress.

Staff represent the NCI on the DHHS Committee to Coordinate Environmental and Related Programs, originally chartered in 1973 as the Department of Health, Education, and Welfare Committee to Coordinate Toxicological Research Programs. This committee was established by the Assistant Secretary for Health as a multiagency group to exchange information on environmental health, toxicology, and related programs. In addition to representatives from each agency in DHHS that supports or conducts these types of programs, there are liaison representatives from the Consumer Products Safety Committee, the EPA, OSHA, CEQ, Library of Congress, Department of Energy, NOAA, Department of Defense, and the NSF. The Committee meets regularly four to six times a year, although it may meet more frequently as the need arises to discuss urgent problems on which the Assistant Secretary or the Department may need advice.

The Interagency Collaborative Group on Environmental Carcinogenesis is an informational committee, chaired by a representative of the NCI's Division of Cancer Etiology, which serves as a forum for exchanging information among member organizations—NCI, NIEHS, the FDA, USDA, the CEQ, NOAA, the National Aeronautics and Space Administration, the Department of Transportation, NSF, and others involved in environmental carcinogenesis research, risk assessment, and regulation.

The NCI also serves on a committee organized by the Office of Science and Technology Policy to develop up-to-date carcinogen science papers. These efforts will include the preparation of a paper on Cancer Principles, for the use and guidance of Federal agencies with the responsibility of making policy guidelines on potential or recognized carcinogens.

The NCI is also involved in developing collaborative activities related to environmental carcinogenesis. The cooperative projects on environmental-occupational cancer are with other Federal agencies (NIEHS, EPA, NIOSH, and OSHA), State agencies, and other institutions. The Division of Cancer Etiology, NCI, manages the NCI-EPA and NCI-NIOSH collaborative programs on environmental and occupational carcinogenesis. The concepts underlying these projects are reviewed by the Divisional Board of Scientific Counselors, and they are managed jointly by co-project officers from NCI and the EPA or NIOSH. Scientific findings from these collaborative efforts are summarized in annual reports and published in peer-reviewed journals.

The NCI also maintains a cooperative agreement with the IARC, which supports a monograph series entitled "Evaluation of the Carcinogenic Risk of Chemicals to Humans." These monographs have become the international reference standard in this field. They are widely used by Federal research and regulatory agencies in the United States for the evaluation of environmental cancer hazards. Other information resources supported by the NCI include an IARC effort to identify and list in an annual bulletin all laboratories in the world involved in carcinogenicity testing and preparation of the PHS-149 Report (Survey of Compounds Which Have Been Tested for Carcinogenicity).

Research in chemical and physical carcinogenesis and in epidemiology is performed by NCI scientists in the intramural program, and extramural research in these areas is supported by the NCI through the traditional R01 and P01 grant mechanism. The NCI also utilizes the RFA mechanism for stimulating research in areas of

particular interest; for example, two RFA were recently issued in the area of chemical carcinogenesis, one entitled "Interspecies Comparisons in Carcinogenesis" and the other entitled "Experimental Studies on Natural Inhibitors of Carcinogenesis." Epidemiologic studies performed or supported by the NCI are aimed at identifying groups at higher or lower risk of developing cancer. Results from these studies suggest that environmental and life-style factors are associated with the disease and thus increase the possibility that a reduction in the incidence of cancer can occur.

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